

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

PERNIX IRELAND PAIN DAC and)	
PERNIX THERAPEUTICS, LLC,)	
)	
Plaintiffs,)	
)	C.A. No. 16-139-WCB
v.)	
)	
ALVOGEN MALTA OPERATIONS LTD.,)	
)	
Defendant.)	PUBLIC VERSION FILED: April 24, 2018

**REPLY BRIEF IN SUPPORT OF PLAINTIFFS’ MOTION FOR SUMMARY
JUDGMENT OF INFRINGEMENT**

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Alvogen's Opposition Brief (D.I. 143) fails to raise any material issue of fact that would preclude granting Pernix's motion. First, Alvogen's argument, that its Label does not encourage the use of its product in patients with mild or moderate hepatic impairment or at an unadjusted dose, is belied by a plain reading of its Label, and its experts, who admitted that its Label encourages infringing uses. Second, Alvogen's assertion that certain claims require two-actors is directly refuted by the *Orexigen* decision, which Alvogen fails to distinguish. Finally, even if two-actors are required, Alvogen fails to raise any material issues of fact that Alvogen's Label encourages infringing uses. There is no factual dispute that when a physician gives a prescription to the patient she/he is directing the patient to take the medication as instructed. All of Alvogen's arguments relate to what occurs after that initial infringement, and even then there is no dispute that the physician can discontinue treatment thereby exercising control. Alvogen's arguments to the contrary are based on a misconstruction of the case law.¹

I. There is No Material Dispute that Alvogen's Label Induces Treatment of Patients with Mild or Moderate Hepatic Impairment

Alvogen asserts that it will not infringe because it does not intend to induce treatment of patients with mild or moderate hepatic impairment. D.I. 143 at 14-18. First, Alvogen argues that because there are substantial noninfringing uses for its product, the "mere knowledge that some users will infringe the asserted claims does not establish intentional inducement." *Id.* at 15. The Federal Circuit has flatly rejected that argument. *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017) ("there is no legal or logical basis" to conclude that because the ANDA product "has substantial noninfringing uses . . . the district court could not permissibly find intent

¹ Alvogen's Opposition Brief included an untimely request for summary judgment of noninfringement. *See, e.g., Kraft Foods Grp. Brands LLC v. TC Heartland, LLC*, No. 14-28-LPS, 2017 U.S. Dist. LEXIS 4607, at *1 n.1 (D. Del. Jan. 12, 2017) (request for summary judgment of noninfringement in answering brief denied as untimely). Alvogen subsequently withdrew its request in a letter to the Court. D.I. 155.

to encourage an infringing use”); *Vanda Pharms. Inc. v. West-Ward Pharms.*, No. 2016-2707, 2018 U.S. App. LEXIS 9360, at *30-31 (Fed. Cir. April 13, 2018) (“even if the proposed ANDA product has ‘substantial noninfringing uses,’ [defendant] may still be held liable for induced infringement”).

Second, Alvogen asserts that statements in its Label relating to hepatic impairment do not evidence intent. D.I. 143 at 16-18. But the Label evidences Alvogen’s specific intent because it “contain[s] directives that will ‘inevitably lead some consumers to practice the claimed method’[.]” *Novartis Pharms. Corp. v. Breckenridge Pharm., Inc.*, 248 F. Supp. 3d 578, 585 (D. Del. 2017); *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017) (“evidence that the product labeling that Defendants seek would inevitably lead some [consumers] to infringe establishes the requisite intent for inducement”); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (finding specific intent where label “would inevitably lead some consumers to practice the claimed method”); *Vanda*, No. 2016-2707, 2018 U.S. App. LEXIS 9360, at *29-30 (“Even if not every practitioner will prescribe an infringing dose, that the target dose range ‘instructs users to perform the patented method’ is sufficient to ‘provide evidence of [defendant’s] affirmative intent to induce infringement.’”); *see also Sanofi v. Glenmark Pharms. Inc.*, 204 F. Supp. 3d 665, 683 (D. Del. 2016).²

Alvogen does not deny that its Label will inevitably lead some patients to infringe—indeed, its Opposition Brief states that “some users will infringe the asserted claims[.]” D.I. 143

² Alvogen notes that in *Eli Lilly*, *AstraZeneca*, and *Sanofi* the finding of specific intent to induce infringement “relied on the instructions in the label, not on the fact that some physicians would infringe.” D.I. 143 at 15-16. Pernix never suggested otherwise. In its Opening Brief, Pernix cited these cases when discussing *direct infringement*, and explained that if Alvogen’s Label induces even some patients to directly infringe, that is sufficient for a finding of specific intent. Pernix established based on undisputed facts that Alvogen’s Label induces infringement by encouraging, recommending, and promoting infringing uses (D.I. 120 at 7, 8, 10, 16, 17).

at 15. And, Alvogen has never disputed that some patients receiving its product will have mild or moderate hepatic impairment. *See* D.I. 120 at Section IV(B)(1). Nor does Alvogen dispute that its Label directs those patients to [REDACTED] *See* D.I. 120 at 8. Alvogen's Label will thus "inevitably lead some" patients with mild or moderate hepatic impairment "to practice the claimed method[s]" by directing them to administer Alvogen's Product. *AstraZeneca*, 633 F.3d at 1060.

In fact, Alvogen's expert admitted that Alvogen's Label promotes infringing use because it includes [REDACTED] in patients with mild or moderate hepatic impairment. D.I. 120 at Section IV(B)(1). As explained more fully below, the Label instructs that [REDACTED] [REDACTED] and that language is repeated in three sections of Alvogen's Label: [REDACTED] [REDACTED] *See* D.I. 120 at 4-5. Thus, Alvogen's Label encourages infringement by repeatedly instructing how to administer Alvogen's Product to the specific claimed population, and as the cases cited above make clear, this shows as a matter of law that Alvogen has the specific intent to induce infringement of these claims.

Nevertheless, based on *Acorda* and *Shire*, Alvogen contends that its Label [REDACTED] [REDACTED] D.I. 143 at 17-18. But *Acorda* and *Shire* are inapposite. In *Acorda*, the claims were directed to reducing somnolence by taking the drug with food, but the label "nowhere sa[id] that somnolence is reduced when capsules are given with food." *Acorda Therapeutics Inc. v. Apotex Inc.*, No. 07-4937-GEB-MCA, 2011 U.S. Dist. LEXIS 102875, at *51-52 (D. Del. Sep. 6, 2011). The Court in *Acorda* concluded that "[a] label devoid of any information directly explaining

reduced somnolence of the capsule with food cannot be said to encourage infringement[.]” *Id.* at *52. In *Shire*, the asserted claims were directed to treating ADHD by taking L-lysine-d-amphetamine with food, and the label indicated that the product could be taken “with or without food[.]” *Shire LLC v. Amneal Pharms, LLC.*, No. 11-3781-SRC, 2014 U.S. Dist. LEXIS 85369, at *15 (D. Del. June 23, 2014). The Court concluded that this statement was “indifferent to which option is selected.” *Id.* at 16.

As shown above, Alvogen’s Label is not “indifferent” and does more than merely describe the use of its product in patients with mild or moderate hepatic impairment—it encourages that use by [REDACTED]

[REDACTED], and [REDACTED]

[REDACTED] Plainly, Alvogen intends that its Product be administered to those types of patients in the manner specified in its Label.

Moreover, Alvogen ignores *GlaxoSmithKline LLC v. Glenmark Pharms., Inc.*, No. 14-877-LPS-CJB, 2017 U.S. Dist. LEXIS 82534 (D. Del. May 23, 2017). There, the claims covered administering carvedilol to reduce mortality in patients with congestive heart failure, and the ANDA product was indicated to reduce mortality in patients “who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq 40\%$ (with or without symptomatic heart failure)[.]” *Id.* at *13, *52. The Court distinguished *Acorda* and *Shire*, explaining that “[i]n explicitly ***instructing doctors to administer*** carvedilol to a patient population that ***includes people with heart failure*** in order to reduce their risk of dying . . . this language cannot really be characterized as being indifferent to the infringing use. And so, it is unlike language indicating that you can take a drug with or without food.” *Id.* at *52 n.12 (emphasis in original). Likewise, Alvogen’s Label undisputedly instructs doctors to administer

Alvogen's Product to a patient population that includes patients with mild or moderate hepatic impairment, and repeatedly instructs how to dose its product to that specific claimed population.

Thus, because Alvogen does not dispute that '760 patent claims 12, 17 and 19 and '499 patent claim 1 will be directly infringed by patients and its arguments as to intent are legally insufficient, Alvogen will infringe those claims as a matter of law. As discussed below, Alvogen's remaining assertions as to the other asserted claims are likewise without merit.

II. There is No Material Dispute that Alvogen's Label Induces the Use of an Unadjusted Dose in '760 Patent Claims 1-4 and 11

Claims 1-4 and 11 include the limitation that the dose "is not adjusted relative to a patient without hepatic impairment[.]" Alvogen's Label specifically encourages the use of an unadjusted dose in the [REDACTED]

[REDACTED] sections. [REDACTED]

[REDACTED]

[REDACTED]

Alvogen incorrectly argues that the above instruction is merely "informational" and "facially does not recommend, promote, or encourage non-adjustment." D.I. 143 at 19. As explained in Pernix's Opening Brief, prior to the patents-in-suit, physicians prescribing opioids reduced the starting dose in patients with hepatic impairment to prevent drug accumulation caused by reduced liver function. D.I. 120 at Section III(A) (citing '760 patent). Performing this adjustment was and is undesirable because it complicates treatment and may inadequately treat the patient's pain. *Id.* Unable to rely on the starting dose known to provide safe and effective pain relief in the normal patient population, physicians instead must monitor each hepatically impaired patient individually while adjusting dosages to try to safely achieve efficacy on a case-by-case basis. *Id.* Alvogen's expert Dr. Schmidt characterized the need for adjustment as a

“recognized problem,” and the patents-in-suit similarly characterize it as a “problem.” Garrett Declaration, Ex. A at ¶134; D.I. 121, Ex. A at 4:30-36, *see also* 2:41-44 (“It is a problem that opioids, including extended release opioids, generally require reduced [*i.e.*, adjusted] dosing in patients with hepatic impairment . . .”). Alvogen’s Label encourages the reader to forego adjusting the dose by instructing that ***there is no need to perform this undesirable and problematic action.*** Consistent with this conclusion, Alvogen’s expert Dr. Candiotti admitted that the instruction [REDACTED] constitutes a “***dosing recommendation***” that “***tells you how to dose***” Alvogen’s Product. D.I. 121, Ex. F at 171:5-12, 173:19-174:12 (emphasis added). And Pernix’s expert Dr. Gudín confirmed that [REDACTED]

[REDACTED]

[REDACTED] Gudín Declaration, Ex. A at ¶81.

Alvogen attempts to downplay the significance of this instruction because it is not found in the [REDACTED] of Alvogen’s Label. D.I. 143 at 4, 16, 18. But Alvogen’s expert Dr. Candiotti testified that “[a] lot of the components of the label are important,” including both the [REDACTED] sections. D.I. 121, Ex. F at 74:7-75:17. And, courts routinely find induced infringement based on sections of an ANDA label other than the [REDACTED]. For example, in *Sanofi v. Glenmark*, the claims recited “administering [a] drug . . . [to] patients who have at least one of six specific cardiovascular risk factors.” *Sanofi*, 204 F. Supp. 3d at 671-72. [REDACTED] of the ANDA label did not identify any of the six claimed risk factors. *Id.* at 675-79. But the Court still found the label induced infringement because “a POSA would read [it] and understand that the FDA-approved use of [the drug] arose out of the [clinical] trial [reported on the label], which involved patients with at least one of the claimed cardiovascular risk

factors,” and the “labels [therefore] will encourage some physicians to prescribe [the drug] to patients with risk factors and will thus inevitably lead to infringing uses.” *Id.* at 678, 680; *see also AstraZeneca*, 633 F.3d at 1047 (finding specific intent based on instructions in Dosage and Administration and Precautions sections); *Vanda*, No. 2016-2707, 2018 U.S. App. LEXIS 9360, at *25-27 (relying on instructions in Dosage and Administration and Pharmacokinetics sections).

III. ’760 Patent Claims 1-4 and 11 Will Be Directly Infringed

A. Patients will directly infringe ’760 patent claims 1-4 and 11

Alvogen does not deny that if the single-actor theory applies, it infringes claims 1-4 and 11 as a matter of law. Rather, Alvogen argues that those claims require two actors, and thus no single actor directly infringes these claims. D.I. 143 at 6-9. Alvogen is mistaken.

Alvogen initially argues that the single-actor theory is new. But for reasons addressed in Pernix’s Opposition to Alvogen’s Motion to Strike, it is not. D.I. 148 at Section III. Alvogen also asserts that Pernix’s position is inconsistent with statements made during claim construction. That too is wrong because during claim construction and in its Opening Brief (D.I. 120), Pernix made clear that the “non-adjustment” limitation is an essential claim limitation. Indeed, meeting that limitation is a prerequisite to administering the product under the claims.

Alvogen’s only substantive argument is that *Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.*, 282 F. Supp. 3d 793 (D. Del. 2017) does not apply because the claim there “referred to an event that occurred in the past[.]” D.I. 143 at 8-9. But the same is true here. The limitation “wherein the dose prescribed to a patient with mild or moderate hepatic impairment when initiating treatment is not reduced” refers to a dose that must be prescribed by the physician *before* the “administering” step of the claim can occur. Alvogen argues that the limitation “explicitly recites a physician’s act of prescribing the dosage unit by using the present tense verb ‘is.’” D.I. 143 at 8. But “is” in the claim refers to “*the dose*”—not the physician’s act of

prescribing. The dose was “not reduced” when the physician prescribed it, and remains (*i.e., is*) unadjusted when the patient takes it. As in *Orexigen*, the limitation of prescribing the product is done “prior to the method being performed” if the claim is construed as having only an “administering” step. 282 F. Supp. 3d at 812.

**B. Patients and physicians will act as a single entity
that directly infringes ’760 patent claims 1-4 and 11**

Even under a joint-infringement interpretation, there is direct infringement as a matter of law. Under this theory, the claims are jointly practiced when a patient with mild or moderate hepatic impairment administers Alvogen’s Product as directed by his or her physician. *See* D.I. 120 at Section IV(C)(2). Alvogen does not deny that when a prescription for its product is handed to a patient, the physician is directing that patient to take the medication as prescribed and thus the claims are being jointly practiced. Rather, Alvogen’s arguments are directed to the continued use of the product, ignoring that joint infringement occurs with the initial prescription given to the patient. Even ignoring that initial infringing act, Alvogen’s assertions are wrong.

First, Alvogen argues that physicians will not condition continued treatment on the patient administering Alvogen’s Product. D.I. 143 at 9-13. Alvogen does not dispute that physicians will enter into written or oral agreements with their patients prior to prescribing Alvogen’s Product, and these agreements will contain statements explaining that, *e.g.*, “[c]ontinuation of the medication is based on evidence of . . . compliance with instructions on[] usage of the medication.” *See* D.I. 120 at Section IV(C)(2). Instead, Alvogen argues that these agreements do not constitute “conditioning” because they are “not contracts.” D.I. 143 at 11. But the Federal Circuit has explicitly rejected the argument that conditioning requires a binding legal contract. *Eli Lilly*, 845 F.3d at 1366-67; *Travel Sentry, Inc. v. Tropp*, 877 F.3d 1370, 1380,

1384-85 (Fed. Cir. 2017) (“In *Eli Lilly*, we rejected the . . . argument that an actor can only condition the performance of a step ‘by imposing a legal obligation to do so’”).

Next, Alvogen argues that the evidence indicates that physicians have discretion whether to terminate treatment in the event that a patient fails to administer Alvogen’s Product as prescribed. *See* D.I. 143 at 10-12. But conditioning does not require an inflexible, “categorical” promise to terminate treatment if a patient fails to administer the drug exactly as directed, as Alvogen suggests. Alvogen relies on *Eli Lilly*, but that decision does not support its position. In *Eli Lilly*, the Federal Circuit found “conditioning” because “[i]f a patient does not take folic acid as instructed, a physician, **in his or her discretion**, need not provide pemetrexed treatment based on the patient’s failure to perform the step of folic acid administration.” 845 F.3d at 1366 (emphasis added). Supporting this conclusion was the label, which instructed patients that “Your doctor **may** . . . delay treatment[.]” *Id.* at 1366; *see also Travel Sentry*, 877 F.3d at 1379-80 (reaffirming that the evidence in *Eli Lilly* “showed that, if a patient does not take folic acid as instructed, then a physician, in his or her discretion, need not provide pemetrexed treatment”).

Last, Alvogen argues that a physician cannot verify that a patient has taken Alvogen’s Product “exactly” as prescribed, and that “conditioning must require at least the possibility of verifying that the condition is met[.]” D.I. 143 at 13. Alvogen cites to no legal authority to support its argument that conditioning requires the possibility of verifying compliance, despite acknowledging that the law does not require a physician to verify compliance or “double-check[] another’s performance[.]” *Id.* (quoting *Eli Lilly*, 845 F.3d at 1366); *see also Travel Sentry*, 877 F.3d at 1380; *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 126 F. Supp. 3d 1037, 1042 (S.D. Ind. 2015) (rejecting argument that physician cannot condition benefit on patient taking medication because “there is no way of knowing whether the patient will or will not actually

take” the medication). As Dr. Gudin testified, physicians check compliance by “ask[ing] each and every visit how [patients] take their medications.” D.I. 144, Ex. 3 at 73:16-21. And, physicians can also conduct a urinalysis to make sure that the patient has been taking the medication. D.I. 120 at 15 n.6. Dr. Candiotti acknowledged this practice and admitted that he has conducted urine tests on patients who have been prescribed opioids. *Id.* Alvogen finally argues that Dr. Gudin admitted that a physician would not know if a patient was taking his or her medication every 10 hours instead of every 12 hours, D.I. 143 at 13, but that is irrelevant because the claimed step only requires administration—not administration every 12 hours.

IV. Conclusion

For the foregoing reasons, Pernix respectfully requests that the Court enter judgment that Alvogen induces infringement of the asserted claims of the '760 and '499 patents.

Respectfully submitted,

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CERTIFICATE OF SERVICE

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